4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2014-N-1721]

Agency Information Collection Activities; Proposed Collection; Comment Request; Investigational New Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing an opportunity for public comment on the proposed collection of certain information by the Agency. Under the Paperwork Reduction Act of 1995 (the PRA), Federal Agencies are required to publish notice in the Federal Register concerning each proposed collection of information, including each proposed extension of an existing collection of information, and to allow 60 days for public comment in response to the notice. This notice solicits comments on regulations under which the clinical investigation of the safety and effectiveness of unapproved new drugs and biological products can be conducted.

DATES: Submit either electronic or written comments on the collection of information by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: Submit electronic comments on the collection of information to http://www.regulations.gov. Submit written comments on the collection of information to the Division of Dockets Management (HFA 305), Food and Drug Administration, 5630 Fishers

Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: FDA PRA Staff, Office of Operations, Food and Drug Administration, 8455 Colesville Rd., COLE-14526, Silver Spring, MD 20993-0002, PRAStaff@fda.hhs.gov.

SUPPLEMENTARY INFORMATION: Under the PRA (44 U.S.C. 3501-3520), Federal Agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. "Collection of information" is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes Agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal Agencies to provide a 60-day notice in the Federal Register concerning each proposed collection of information, including each proposed extension of an existing collection of information, before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth in this document.

With respect to the following collection of information, FDA invites comments on these topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Investigational New Drug (IND) Regulations--21 CFR Part 312 (OMB Control Number 0910-0014)--Extension

FDA is requesting OMB approval for the reporting and recordkeeping requirements contained in FDA regulations entitled "Investigational New Drug Application" in 21 CFR part 312 (part 312). Part 312 implements provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) (the FD&C Act) to issue regulations under which the clinical investigation of the safety and effectiveness of unapproved new drugs and biological products can be conducted.

FDA is charged with implementing statutory requirements that drug products marketed in the United States be shown to be safe and effective, properly manufactured, and properly labeled for their intended uses. Section 505(a) of the FD&C Act provides that a new drug may not be introduced or delivered for introduction into interstate commerce in the United States unless FDA has previously approved a new drug application (NDA). FDA approves an NDA only if the sponsor of the application first demonstrates that the drug is safe and effective for the conditions prescribed, recommended, or suggested in the product's labeling. Proof must consist, in part, of adequate and well-controlled studies, including studies in humans, that are conducted by qualified experts. The IND regulations establish reporting requirements that include an initial application as well as amendments to that application, reports on significant revisions of clinical investigation plans, and information on a drug's safety or effectiveness. In addition, the sponsor is required to give FDA an annual summary of the previous year's clinical experience.

Submissions are reviewed by medical officers and other Agency scientific reviewers assigned responsibility for overseeing the specific study. The IND regulations also contain recordkeeping requirements that pertain to the responsibilities of sponsors and investigators. The

detail and complexity of these requirements are dictated by the scientific procedures and human subject safeguards that must be followed in the clinical tests of investigational new drugs.

The IND information collection requirements provide the means by which FDA can monitor the clinical investigation of the safety and effectiveness of unapproved new drugs and biological products, including the following: (1) Monitor the safety of ongoing clinical investigations; (2) determine whether the clinical testing of a drug should be authorized; (3) ensure production of reliable data on the metabolism and pharmacological action of the drug in humans; (4) obtain timely information on adverse reactions to the drug; (5) obtain information on side effects associated with increasing doses; (6) obtain information on the drug's effectiveness; (7) ensure the design of well-controlled, scientifically valid studies; (8) obtain other information pertinent to determining whether clinical testing should be continued, and information related to the protection of human subjects. Without the information provided by industry as required under the IND regulations, FDA cannot authorize or monitor the clinical investigations which must be conducted prior to authorizing the sale and general use of new drugs. These reports enable FDA to monitor a study's progress, to assure subject safety, to assure that a study will be conducted ethically, and to increase the likelihood that the sponsor will conduct studies that will be useful in determining whether the drug should be marketed and available for use in medical practice.

There are two forms that are required under part 312:

Form FDA-1571--"Investigational New Drug Application." A person who intends to conduct a clinical investigation submits this form to FDA. It includes the following information: (1) A cover sheet containing background information on the sponsor and investigator; (2) a table of contents; (3) an introductory statement and general investigational plan; (4) an investigator's

brochure describing the drug substance; (5) a protocol for each planned study; (6) chemistry, manufacturing, and control information for each investigation; (7) pharmacology and toxicology information for each investigation; and (8) previous human experience with the investigational drug.

Form FDA-1572--"Investigator Statement." Before permitting an investigator to begin participation in an investigation, the sponsor must obtain and record this form. It includes background information on the investigator and the investigation, and a general outline of the planned investigation and the study protocol.

FDA is requesting OMB approval for the following reporting and recordkeeping requirements in part 312.

I. Reporting Requirements

21 CFR 312.2(e)--Requests for FDA advice on the applicability of part 312 to a planned clinical investigation.

21 CFR 312.6--Labeling of an investigational new drug. Estimates for the information collection in this requirement are included under § 312.23(a)(7)(iv)(d).

21 CFR 312.8--Charging for investigational drugs under an IND.

21 CFR 312.10--Applications for waiver of requirements under part 312. As indicated in § 312.10(a), estimates for the information collection in this requirement are included under §§ 312.23 and 312.31. In addition, other waiver requests under § 312.10 are estimated in table 1.

21 CFR 312.20(c)--Applications for investigations involving an exception from informed consent under § 50.24 (21 CFR 50.24). Estimates for the information collection in this requirement are included under § 312.23.

21 CFR 312.23--IND (content and format).
.23(a)(1) -- Cover sheet FDA-1571.
.23(a)(2) --Table of Contents.
.23(a)(3) -- Investigational plan for each planned study.
.23(a)(5) -- Investigator's brochure.
.23(a)(6) -- Protocols - Phase 1, 2, and 3.
.23(a)(7) -- Chemistry, manufacturing, and control information.

.23(a)(7)(iv)(a),(b),(c) -- A description of the drug substance, a list of all components, and any placebo used.
.23(a)(7)(iv)(d) -- Labeling: Copies of labels and labeling to be provided each investigator.
.23(a)(7)(iv)(e) -- Environmental impact analysis regarding drug manufacturing and use.
.23(a)(8) -- Pharmacological and toxicology information.
.23(a)(9) -- Previous human experience with the investigational drug.
.23(a)(10) -- Additional information.
.23(a)(11) -- Relevant information.
.23(f) -- Identification of exception from informed consent.

21 CFR 312.30--Protocol amendments.
.30(a) -- New protocol
.30(b) -- Changes in protocol
.30(c) -- New investigator.
.30(d) -- Content and format.
.30(e) -- Frequency.

21 CFR 312.31--Information amendments.
.31(b) -- Content and format.
-- Chemistry, toxicology, or technical information.

21 CFR 312.32--Safety reports.
.32(c)(1) -- Written reports to FDA and to investigators.
.32(c)(2) -- Telephone reports to FDA for fatal or life-threatening experience.
.32(c)(3) -- Format or frequency.
.32(d) -- Followup submissions.

21 CFR 312.33--Annual reports.
.33(a) -- Individual study information.
.33(b) -- Summary information.
(b)(1) -- Adverse experiences.
(b)(2) -- Safety report summary.
(b)(3) -- List of fatalities and causes of death.
(b)(4) -- List of discontinuing subjects.
(b)(5) -- Drug action.
(b)(6) -- Preclinical studies and findings.
(b)(7) -- Significant changes.
.33(c) -- Next year general investigational plan.
.33(d) -- Brochure revision.
.33(e) -- Phase I protocol modifications.
.33(f) -- Foreign marketing developments.

21 CFR 312.38(b) and (c)--Notification of withdrawal of an IND.

21 CFR 312.41--Comment and advice on an IND. Estimates for the information collection in

this requirement are included under § 312.23.

21 CFR 312.42--Sponsor requests that a clinical hold be removed, and submits a complete response to the issues identified in the clinical hold order.

21 CFR 312.44(c) and (d)--Opportunity for sponsor response to FDA when IND is terminated.

21 CFR 312.45(a) and (b)--Sponsor request for, or response to, an inactive status determination of an IND.

21 CFR 312.47--Meetings, including "End-of-Phase 2" meetings and "Pre-NDA" meetings.

21 CFR 312.48--Dispute resolution. Estimates for the information collection in this requirement are included under § 312.47.

21 CFR 312.53(c)--Investigator information. Investigator report (Form FDA-1572) and narrative; Investigator's background information; Phase 1 outline of planned investigation and Phase 2 outline of study protocol.

21 CFR 312.54(a) and (b)--Sponsor submissions concerning investigations involving an exception from informed consent under § 50.24.

21 CFR 312.55(b)--Sponsor reports to investigators on new observations, especially adverse reactions and safe use. Only "new observations" are estimated under this section; investigator brochures are included under § 312.23.

21 CFR 312.56(b), (c), and (d)--Sponsor monitoring of all clinical investigations, investigators, and drug safety; notification to FDA and others.

21 CFR 312.58(a)--Sponsor's submission of records to FDA on request.

21 CFR 312.64--Investigator reports to the sponsor.
.64(a) -- Progress reports.
.64(b) -- Safety reports
.64(c) -- Final reports.
.64(d) – Financial disclosure reports.

21 CFR 312.66--Investigator reports to institutional review board (IRB). Estimates for the information collection in this requirement are included under § 312.53.

21 CFR 312.70--Investigator disqualification; opportunity to respond to FDA.

21 CFR 312.83--Sponsor submission of treatment protocol. Estimates for this requirement are included under § 312.320.

21 CFR 312.85--Sponsors conducting phase 4 studies. Estimates for the information collection in this requirement are included under § 312.23, and under §§ 314.50, 314.70, and 314.81 in OMB control number 0910-0001.

21 CFR 312.110(b)--Requests to export an investigational drug.

21 CFR 312.120--Submissions related to foreign clinical studies not conducted under an IND.

21 CFR 312.130--Requests for disclosable information in an IND and from investigations involving an exception from informed consent under § 50.24.

21 CFR 312.310(b); 312.305(b)--Submissions related to expanded access and treatment of an individual patient.

21 CFR 312.310(d)--Submissions related to emergency use of an investigational new drug.

21 CFR 312.315(c); 312.305(b)--Submissions related to expanded access and treatment of an intermediate-size patient population.

21 CFR 312.320--Submissions related to a treatment IND or treatment protocol.

II. Recordkeeping Requirements

21 CFR 312.52(a)--Transfer of obligations to a contract research organization.

21 CFR 312.57--Sponsor recordkeeping on the investigational drug.

21 CFR 312.59--Sponsor recordkeeping of disposition of unused supply of drugs. Estimates for the information collection in this requirement are included under § 312.57.

21 CFR 312.62(a)--Investigator recordkeeping of disposition of drugs.

21 CFR 312.62(b)--Investigator recordkeeping of case histories of individuals.

21 CFR 312.120(d)--Recordkeeping requirements for submissions related to foreign clinical studies not conducted under an IND. Estimates for the information collection in this requirement are included under § 312.57.

21 CFR 312.160(a)(3)--Records pertaining to the shipment of drugs for investigational use in laboratory research animals or in vitro tests.

21 CFR 312.160(c)--Shipper records of alternative disposition of unused drugs.

FDA estimates the burden of this collection of information as follows:

Table 1.--Estimated Annual Reporting Burden for Human Drugs[1]

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
312.2(e) Requests for FDA advice on the applicability of part 312 to a planned clinical investigation.	800	1	800	24	19,200
312.8 Requests to charge for an investigational drug.	56	1.25	70	48	3,360
312.10 Requests to waive a requirement in part 312.	50	1.76	88	24	2,112
312.23(a) through (f) IND content and format (including Form FDA 1571)	1,689	1.57	2,648	1,600	4,236,800
312.30(a) through (e) Protocol amendments.	3,739	5.77	21,588	284	6,130,992
312.31 (b) Information amendments.	4,537	3.39	15,377	100	1,537,700
312.32(c) and (d) IND Safety reports.	755	24.28	18,332	32	586,624
312.33(a) through (f) IND Annual reports.	2,877	2.76	7,953	360	2,863,080
312.38(b) and (c) Notifications of withdrawal of an IND.	862	1.54	1,328	28	37,184
312.42 Sponsor requests that a clinical hold be removed, including sponsor submission of a complete response to the issues identified in the clinical hold order.	158	1.30	205	284	58,220
312.44(c) and (d) Sponsor responses to FDA when IND is terminated.	12	1	12	16	192
312.45(a) and (b) Sponsor requests for or responses to an inactive status determination of an IND by FDA.	260	1.73	451	12	5,412
312.47 Meetings, including "End-of-Phase 2" meetings and "Pre-NDA" meetings.	225	1.86	419	160	67,040
312.53(c) Investigator reports submitted to the sponsor, including Form FDA 1572, curriculum vitae,	1,444	8.38	12,087	80	966,960

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
clinical protocol, and financial disclosure. (Third party disclosure)					
312.54(a) Sponsor submissions to FDA concerning investigations involving an exception from informed consent under 21 CFR 50.24.	7	5	35	48	1,680
312.54(b) Sponsor notifications to FDA and others concerning an IRB determination that it cannot approve research because it does not meet the criteria in the exception from informed consent in § 50.24(a). (Includes third party disclosure)	7	1	7	48	336
312.55(a) Investigator brochures submitted by the sponsor to each investigator. (Third party disclosure)	590	3.50	2,067	48	99,216
312.55(b) Sponsor reports to investigators on new observations, especially adverse reactions and safe use. (Third party disclosure)	590	3.50	2,067	48	99,216
312.56(b),(c), and (d) Sponsor notifications to FDA and others resulting from: (1) The sponsor's monitoring of all clinical investigations and determining that an investigator is not in compliance with the investigation agreements; (2) the sponsor's review and evaluation of the evidence relating to the safety and effectiveness of the investigational drug; and (3) the sponsor's determination that the investigational drug presents an unreasonable and significant risk to subjects. (Includes third party disclosure)	3,584	6.52	23,355	80	1,868,400

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
312.58(a) Sponsor's submissions of clinical investigation records to FDA on request during FDA inspections.	60	1	60	8	480
312.64 Investigator reports to the sponsor, including progress reports, safety reports, final reports, and financial disclosure reports. (Third party disclosure)	1,444	1	1,444	24	34,656
312.70 During the disqualification process of a clinical investigator by FDA, the number of investigator responses or requests to FDA following FDA's notification to an investigator of its failure to comply with investigation requirements.	4	1	4	40	160
312.110(b)(4) and (b)(5) Written certifications and written statements submitted to FDA relating to the export of an investigational drug.	11	26.28	289	75	21,675
312.120(b) Submissions to FDA of "supporting information" related to the use of foreign clinical studies not conducted under an IND.	1,414	8.63	12,198	32	390,336
312.120(c) Waiver requests submitted to FDA related to the use of foreign clinical studies not conducted under an IND.	35	2.34	82	24	1,968
312.130 Requests for disclosable information in an IND and for investigations involving an exception from informed consent under § 50.24.	3	1	3	8	24
312.310(b) and 312.305(b) Submissions related to expanded access and treatment of an individual patient.	228	1.76	401	8	3,208
312.310(d) Submissions related to	410	2.19	899	16	14,384

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
emergency use of an investigational new drug.					
312.315(c) and 312.305(b) Submissions related to expanded access and treatment of an intermediate-size patient population.	44	7.07	311	120	37,320
312.320(b) Submissions related to a treatment IND or treatment protocol.	12	12.67	152	300	45,600
Total					19,134,039

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 2.--Estimated Annual Recordkeeping Burden for Human Drugs[1]

21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
312.52(a) Sponsor records for the transfer of obligations to a contract research organization.	335	1.50	503	2	1,006
312.57 Sponsor recordkeeping showing the receipt, shipment, or other disposition of the investigational drug, and any financial interests.	1,689	1	1,689	100	168,900
312.62(a) Investigator recordkeeping of the disposition of drugs.	1,444	1	1,444	40	57,760
312.62(b) Investigator recordkeeping of case histories of individuals.	1,444	1	1,444	40	57,760
312.160(a)(3) Records pertaining to the shipment of drugs for investigational use in laboratory research animals or in vitro tests.	547	1.40	782	0.50 (30 minutes)	391
312.160(c) Shipper records of alternative disposition of unused drugs.	547	1.40	782	0.50 (30 minutes)	391
Total					286,190

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 3.--Estimated Annual Reporting Burden for Biologics[1]

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
312.2(e) Requests for FDA advice on the applicability of part 312 to a planned clinical investigation.	217	1.18	255	24	6,120
312.8 Requests to charge for an investigational drug.	20	1.50	30	48	1,440
312.10 Requests to waive a	2	1	2	24	48

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
requirement in part 312.					
312.23(a) through (f) IND content and format.	335	1.35	452	1,600	723,200
312.30(a) through (e) Protocol amendments.	694	5.84	4,050	284	1,150,200
312.31 (b) Information amendments.	77	2.43	187	100	18,700
312.32(c) and (d) IND Safety reports.	161	8.83	1,421	32	45,472
312.33(a) through (f) IND Annual reports.	745	2.14	1,595	360	574,200
312.38(b) and (c) Notifications of withdrawal of an IND.	134	1.69	227	28	6,356
312.42 Sponsor requests that a clinical hold be removed, including sponsor submission of a complete response to the issues identified in the clinical hold order.	67	1.30	87	284	24,708
312.44(c) and (d) Sponsor responses to FDA when IND is terminated.	34	1.15	39	16	624
312.45(a) and (b) Sponsor requests for or responses to an inactive status determination of an IND by FDA.	55	1.38	76	12	912
312.47 Meetings, including "End-of-Phase 2" meetings and "Pre-NDA" meetings.	88	1.75	154	160	24,640
312.53(c) Investigator reports submitted to the sponsor, including Form FDA-1572, curriculum vitae, clinical protocol, and financial disclosure.	453	6.33	2,869	80	229,520
312.54(a) Sponsor submissions to FDA concerning investigations involving an exception from informed consent under § 50.24.	1	1	1	48	48
312.54(b) Sponsor notifications to FDA and others concerning an IRB determination that it cannot approve research because it	1	1	1	48	48

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
does not meet the criteria in the exception from informed consent in § 50.24(a).					
312.55(a) Number of investigator brochures submitted by the sponsor to each investigator.	239	1.91	457	48	21,936
312.55(b) Number of sponsor reports to investigators on new observations, especially adverse reactions and safe use.	243	4.95	1,203	48	57,744
312.56(b),(c), and (d) Sponsor notifications to FDA and others resulting from: (1) The sponsor's monitoring of all clinical investigations and determining that an investigator is not in compliance with the investigation agreements; (2) the sponsor's review and evaluation of the evidence relating to the safety and effectiveness of the investigational drug; and (3) the sponsor's determination that the investigational drug presents an unreasonable and significant risk to subjects.	108	2.21	239	80	19,120
312.58(a) Number of sponsor's submissions of clinical investigation records to FDA on request during FDA inspections.	7	1	7	8	56
312.64 Number of investigator reports to the sponsor, including progress reports, safety reports, final reports, and financial disclosure reports.	2,728	3.82	10,411	24	249,864
312.70 During the disqualification process of a clinical investigator by FDA, the number of investigator responses or requests to FDA following FDA's notification to an investigator of its failure to comply with investigation	5	1	5	40	200

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
requirements.					
312.110(b)(4) and (b)(5) Number of written certifications and written statements submitted to FDA relating to the export of an investigational drug.	18	1	18	75	1,350
312.120(b) Number of submissions to FDA of "supporting information" related to the use of foreign clinical studies not conducted under an IND.	280	9.82	2,750	32	88,000
312.120(c) Number of waiver requests submitted to FDA related to the use of foreign clinical studies not conducted under an IND.	7	2.29	16	24	384
312.130 Number of requests for disclosable information in an IND and for investigations involving an exception from informed consent under § 50.24.	350	1.34	470	8	3,760
312.310(b) and 312.305(b) Number of submissions related to expanded access and treatment of an individual patient.	78	1.08	84	8	672
312.310(d) Number of submissions related to emergency use of an investigational new drug.	76	2.76	210	16	3,360
312.315(c) and 312.305(b) Number of submissions related to expanded access and treatment of an intermediate-size patient population.	9	1	9	120	1,080
312.320(b) Number of submissions related to a treatment IND or treatment protocol.	1	1	1	300	300
Total					3,254,062

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 4.-- Estimated Annual Recordkeeping Burden for Biologics[1]

21 CFR Section	No. of Recordkeepers	No. of Records per	Total Annual	Average Burden per	Total Hours

		Recordkeeper	Records	Recordkeeping	
312.52(a) Sponsor records for the transfer of obligations to a contract research organization.	75	1.40	105	2	210
312.57 Sponsor recordkeeping showing the receipt, shipment, or other disposition of the investigational drug, and any financial interests.	335	2.70	904	100	90,400
312.62(a) Investigator recordkeeping of the disposition of drugs.	453	1	453	40	18,120
312.62(b) Investigator recordkeeping of case histories of individuals.	453	1	453	40	18,120
312.160(a)(3) Records pertaining to the shipment of drugs for investigational use in laboratory research animals or in vitro tests.	111	1.40	155	0.50 (30 minutes)	78
312.160(c) Shipper records of alternative disposition of unused drugs.	111	1.40	155	0.50 (30 minutes)	78
Total					127,006

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Dated: October 31, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

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